

**Remarks**

Claims 15, 16, 18 and 19 were amended to reflect proper antecedent basis. No new matter has been introduced by these amendments.

Applicants note that the subject application was transferred to Examiner Sharareh after the issuance of an Advisory Action by Examiner Jiang. Applicants appreciate the time taken by Examiner Sharareh to discuss with Applicants' undersigned representative the pending claims in light of references cited by Examiner Jiang in the Final Office Action dated August 8, 2005.

**1. Rejection under 35 U.S.C. § 103(a)**

In an Advisory Action dated November 30, 2005, Examiner Jiang indicated that the rejection of claims 14-30 as allegedly being rendered obvious over U.S. Patent 5,792,635 or U.S. Patent 5,842,740 in view of the Merck Manual of Diagnosis and Therapy was maintained from the Final Office Action dated August 8, 2005.

In the Final Office Action, the Examiner asserted that U.S. Patents 5,792,635 and 5,842,740 describe the use of compound 1436 as an anti-arteriosclerotic and for the treatment of diabetes. The Examiner acknowledged that neither these patents expressly discloses the use of aminosterols for treating serum cholesterol or for reducing blood cholesterol levels in a mammal but relied on the Merck Manual for allegedly teaching that elevated serum cholesterol, hypertension diabetes mellitus and obesity are the major risk factors for atherosclerosis. Thus, according to the Examiner, it would have been obvious to a person of ordinary skill in the art to employ the particular aminosterols described in U.S. Patents 5,792,635 and 5,842,740 for treating serum cholesterol or reducing blood cholesterol levels in a mammal.

Applicants respectfully disagree with the Examiner's assessment and applicability of the disclosures of U.S. Patents 5,792,635 and 5,842,740 in view of the Merck Manual, to the claimed invention for at least the reasons discussed below.

Applicants attempted to bring to Examiner Jiang's attention and now point out to Examiner Sharareh that U.S. Patent 5,842,740 is not pertinent to any aspect of Applicants' claimed invention. The Examiner may have intended to cite U.S. Patent 5,840,740, which has at least one of the same inventors, Zasloff, as the subject application. For the purposes of this response, Applicants will presume that it is U.S. Patent 5,840,740 that has been cited by the Examiner.

Reducing Blood Glucose Levels

U.S. Patents 5,792,635 and 5,840,740 both teach the use of aminosterols for raising blood glucose levels in mammals. Data obtained from an experiment in which normal mice, with only a genetic predisposition for diabetes, were administered various aminosterols, indicated that "blood glucose levels were elevated between 2-3 fold normal after administration of these steroids." See column 83, lines 17-64 of U.S. Patent 5,792,635 and column 79, line 29 to column 80, line 8 of U.S. Patent 5,840,740. The conclusion drawn from this observation was that the hyperglycemic response resulted from inhibition of insulin secretion. "Thus, the long-term chronic administration of a compound such as compound 1436 may be of value in preventing or delaying the onset of both Type I and Type II diabetes." After reading either of U.S. Patents 5,792,635 and 5,840,740, a person of ordinary skill in the art would be motivated to use aminosterols strictly for preventing or delaying the onset of diabetes. Because aminosterols were observed to increase glucose levels, these patents would actually teach against using aminosterols in persons suffering from diabetes, since elevated blood glucose levels are often indicative of diabetes.

In contrast, Applicants have unexpectedly discovered that aminosterols decrease glucose levels in mammals suffering from diabetes. See, for example, Example 2 of Applicants' specification and the accompanying Table 1, which shows that in diabetic mice treated with aminosterol 1436, blood glucose levels were only 53.5 mg/dl, compared to 465.0 mg/dl in untreated diabetic mice. Therefore, Applicants' claims directed to reducing blood glucose levels in a diabetic mammal comprising administration of an aminosterol of the recited formula, is clearly unobvious in view of U.S. Patents 5,792,635 and 5,840,740. For at least the above-discussed reasons, Applicants respectfully request that this rejection be withdrawn.

Reducing Blood Cholesterol Levels

The Examiner rejects Applicants' claims directed to reducing blood cholesterol levels because U.S. Patents 5,792,635 and 5,840,740 allegedly describe the use of compound 1436 as an anti-arteriosclerotic and because the Merck Manual allegedly teaches that elevated serum cholesterol is a major risk factor for atherosclerosis.

Applicants point out to the Examiner that the Merck Manual defines arteriosclerosis as a "generic term for several diseases in which the arterial wall becomes thickened and loses elasticity" (page 1654) (emphasis added). Atherosclerosis is defined by the Merck Manual as "a form of arteriosclerosis characterized by patchy subintimal thickening (atheromas) of medium and large arteries, which can reduce or obstruct blood flow" (page 1655). Therefore, as defined by the Merck Manual, "arteriosclerosis" is not

the same as "atherosclerosis" because arteriosclerosis is a term encompassing several diseases (and likely several different causes for disease), while atherosclerosis is a particular form of arteriosclerosis. U.S. Patents 5,792,635 and 5,840,740 refer only to anti-arteriosclerotic agents and do not teach or suggest the narrower anti-atherosclerotic agents. Thus, a person of ordinary skill in the art would not be motivated with an expectation of success to prepare aminosterols for reducing blood cholesterol levels based on a sentence in these patents indicating that various NHE-specific inhibitors may provide anti-arteriosclerotic agents. This is especially true since undoubtedly at least some manifestations of arteriosclerosis are not due to elevated levels of blood cholesterol.

Further, treatment of a risk factor is not the same as treating a disease state that may have resulted, in part, from the risk factor. Elevated blood cholesterol levels are associated with many diseases and/or pathological states, including stroke, myocardial infarction, Cushing's syndrome, Alstrom syndrome, diabetes, Amaurosis fugax, hypervitaminosis, *etc.* Thus, it would not be obvious to a person of ordinary skill in the art to assume that just because a compound may be effective in treating a disease state, that it would necessarily also be effective in preventing or treating a particular symptom (*e.g.*, elevated blood cholesterol levels) that may eventually lead to the expression of that disease state. For at least these reasons, Applicants request that this rejection be withdrawn.

2. **Conclusion**

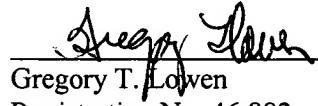
Upon consideration of the foregoing, it will be recognized that Applicants have fully and appropriately responded to all of the Examiner's rejections. Accordingly, the claims are believed to be in proper form in all respects and a favorable action on the merits is respectfully requested.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a

**CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,

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